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1444 7590 06/11/2009

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, NW
SUITE 300
WASHINGTON, DC 20001-5303

EXAMINER	
STAPLES, MARK	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 06/11/2009

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,405	09/30/2005	Andrea Cossarizza	COSSARIZZA-1	5546

TITLE OF INVENTION: METHOD OF DETERMINING THE COPY NUMBER OF A NUCLEOTIDE SEQUENCE

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1510	$300	$0	$1810	09/11/2009

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

1444 7590 06/11/2009

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Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,405	09/30/2005	Andrea Cossarizza	COSSARIZZA-1	5546

TITLE OF INVENTION: METHOD OF DETERMINING THE COPY NUMBER OF A NUCLEOTIDE SEQUENCE

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nonprovisional	NO	$1510	$300	$0	$1810	09/11/2009

EXAMINER	ART UNIT	CLASS-SUBCLASS
STAPLES, MARK	1637	435-091200

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

❑ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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STAPLES, MARK	
ART UNIT	PAPER NUMBER
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DATE MAILED: 06/11/2009

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 08/07) Approved for use through 08/31/2010.

Notice of Allowability	Application No.	Applicant(s)	
	10/522,405	COSSARIZZA, ANDREA	
	Examiner	Art Unit	
	MARK STAPLES	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *05/26/2009*.

2. ☒ The allowed claim(s) is/are *1-28*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *06/05/2009* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

/Kenneth R Horlick/ Primary Examiner, Art Unit 1637	/M. S./, Mark Staples Examiner, Art Unit 1637 June 5, 2009

DETAILED ACTION

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Attorney Livnat on 06/05/2009.

The application has been amended as follows. Claims 1, 2, 17, and 24-28 are amended as follows.

1. ***(currently** amended)* A method of determining the relative copy number (CN) of a first nucleotide sequence I (NucSeqI) in a test sample using an amplification technique, said method comprising the steps of:

(1) adding to the test sample that comprises NucSeqI and a chromosome-derived second nucleotide sequence II (NucSeqII), the following ingredients:

- nucleotides,
- primers,
- polymerase,
- a first probe specific to NucSeqI, comprising a first fluorophore and a quencher, and/or a second probe specific to NucSeqII comprising a second fluorophore and a quencher, wherein the first fluorophore and the second fluorophore are different; and optionally
- any additional reagents required for amplification.

(2) carrying out the following amplification steps in one or more amplification cycles:

(a) amplifying NucSeqI in said test sample,

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(b) amplifying NucSeqII in said test sample,

(c) in a control sample, to which said ingredients of (1) are added, amplifying at multiple dilutions a third nucleotide sequence I' (NucSeqI') corresponding to NucSeqI to which said first probe is also specific, in the presence of said first probe,

wherein the relationship of NucSeqI and NucSeqI' is defined as

(A) NucSeqI hybridizes to the complement of NucSeqI', and

(B) NucSeqI' hybridizes to the complement of NucSeqI,

both under stringent hybridization conditions, and, if NucSeqI and NucSeqI' differ in length, the shorter of the two is at most 30% shorter than the other; and

(d) in a control sample, to which said ingredients of (1) are added, amplifying at multiple dilutions a fourth nucleotide sequence II' (NucSeqII') corresponding to NucSeqII to which said second probe is also specific, in the presence of said second probe,

wherein the relationship of NucSeqII and NucSeqII' is defined as

(A) NucSeqII hybridizes to the complement of NucSeqII', and

(B) NucSeqII' hybridizes to the complement of NucSeqII,

both under stringent hybridization conditions, and, if NucSeqII and NucSeqII' differ in length, the shorter of the two is, at most, 30% shorter than the other;

wherein

(i) NucSeqI' and NucSeqII' are both localized on a single vector in which the ratio of NucSeqI' to NucSeqII' is known,

(ii) standard curves SC_I and SC_{II} comprising at least two reference points are generated by amplification of NucSeqI' and NucSeqII', respectively, at multiple dilutions, wherein the starting quantity, concentration or dilution of NucSeqI' and NucSeqII" is known, and

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(iii) at least one pair of amplification reactions (a) and (b) or (c) and (d) is performed in a single container and monitored by fluorescence during amplification;

(3) determining the results of the amplifications of step (2) expressed as threshold cycle (Ct) as a function of said starting quantity, concentration or dilution;

(4) obtaining from the results in step (3) the following values:

(i) "Conc-I_{SCI}" which is the concentration, [[or]] quantity or dilution in the test sample of NucSeqI determined from standard curve SC_I; and

(ii) "Conc-II_{SCII}" which is the concentration, [[or]] quantity or dilution in the test sample of NucSeqII determined from standard curve SC_{II},

which standard curves express threshold cycle as a function of said starting concentration, [[or]] quantity or dilution; and

(5) determining from the values obtained in step (4) the relative CN of NucSeqI with respect to NucSeqII by the formula:

$$\text{Relative CN} = \frac{\text{Conc-}I_{SCI}}{\text{Conc-}II_{SCII}}$$

thereby determining the relative CN of NucSeqI in said test sample.

2. ***(currently** amended)* A method for determining the absolute CN of a nucleotide sequence NucSeqI in a test sample, comprising:

(a) determining the relative CN using the method of claim 18, and

(b) multiplying the relative CN by the absolute CN of NucSeqII per cell.

17. ***(currently** amended)* A method according to claim 1, wherein the test sample is derived from cells.

24. ***(currently** amended)* A method of determining the relative CN of a first nucleotide sequence I (NucSeqI) in a test sample using an amplification technique, said method comprising the steps of:

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(1) adding to the test sample that comprises NucSeqI and a second nucleotide sequence II (NucSeqII), the following ingredients:

- nucleotides,
- primers,
- polymerase,
- a first probe specific to NucSeqI , comprising a first fluorophore and a quencher, and/or a second probe specific to NucSeqII comprising a second fluorophore and a quencher, wherein the first fluorophore and the second fluorophore are different; and optionally
- any additional reagents required for amplification,

(2) carrying out the following amplification steps in one or more amplification cycles:

(a) amplifying NucSeqI in said test sample,

(b) amplifying NucSeqII in said test sample,

(c) in a control sample, to which said ingredients of (1) are added, amplifying at multiple dilutions a third nucleotide sequence I' (NucSeqI') corresponding to NucSeqI to which said first probe is also specific, in the presence of said first probe,

wherein the relationship of NucSeqI and NucSeqI' is defined as

(A) NucSeqI hybridizes to the complement of NucSeqI', and

(B) NucSeqI' hybridizes to the complement of NucSeqI,

both under stringent hybridization conditions, and, if NucSeqI and NucSeqI' differ in length, the shorter of the two is at most 30% shorter than the other; and

(d) in a control sample, to which said ingredients of (1) are added, amplifying at multiple dilutions a fourth nucleotide sequence II' (NucSeqII') corresponding to NucSeqII to which said second probe is also specific, in the presence of said second probe,

wherein the relationship of NucSeqII and NucSeqII' is defined as

(A) NucSeqII hybridizes to the complement of NucSeqII', and

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(B) NucSeqII' hybridizes to the complement of NucSeqII, both under stringent hybridization conditions, and, if NucSeqII and NucSeqII' differ in length, the shorter of the two is, at most, 30% shorter than the other;

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wherein

(i) NucSeqI' and NucSeqII' are both localized on a single vector in which the ratio of NucSeqI' to NucSeqII' is known,

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(ii) standard curves SC_I and SC_{II} comprising at least two reference points are generated by amplification of NucSeqI' and NucSeqII', respectively, at multiple dilutions, wherein the starting quantity, concentration or dilution of NucSeqI' and NucSeqII' is known, and

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(iii) at least one pair of amplification reactions (a) and (b) or (c) and (d) is performed in a single container and monitored by fluorescence during amplification;

(3) determining the results of the amplifications of step (2) expressed as threshold cycle (Ct) as a function of said starting quantity, concentration or dilution;

(4) obtaining from the results in step (3) the following values:

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(i) "Conc-I_{SCI}" which is the concentration, [[or]] quantity or dilution in the test sample of NucSeqI determined from standard curve SC_I; and

(ii) "Conc-II_{SCII}" which is the concentration, [[or]] quantity or dilution in the test sample of NucSeqII determined from standard curve SC_{II},

which standard curves express threshold cycle as a function of said starting concentration, [[or]] quantity or dilution; and

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(5) determining from the values obtained in step (4) the relative CN of NucSeqI with respect to NucSeqII by the formula:

$$\text{Relative CN} = \frac{\text{Conc-}I_{SCI}}{\text{Conc-}II_{SCII}}$$

thereby determining the relative CN of NucSeqI in said test sample.

25. ***(currently** amended)* The method of claim 1 wherein the quantity in the test sample in step (4) is the number of copies of NucSeqI or NucSeqII obtained from the respective standard curves in which the quantity or relative dilution of NucSeqI' or NucSeqII', expressed as copy number, is plotted on the X-axis.

26. ***(currently** amended)* The method of claim 1 wherein the concentration in the test sample in step (4) is the molar or weight concentration of NucSeqI or NucSeqII obtained from the respective standard curves in which the concentration or relative dilution of NucSeqI' or NucSeqII' is plotted on the X-axis.

27. ***(currently** amended)* The method of claim 24, wherein the quantity in the test sample in step (4) is the number of copies of NucSeqI or NucSeqII obtained from the respective standard curves in which the quantity or relative dilution of NucSeqI' or NucSeqII', expressed as copy number, is plotted on the X-axis.

28. ***(currently** amended)* The method of claim 24, wherein the concentration in the test sample in step (4) is the molar or weight concentration of NucSeqI or NucSeqII obtained from the respective standard curves in which the concentration or relative dilution of NucSeqI' or NucSeqII' is plotted on the X-axis.

Allowable Subject Matter

2. Claims 1-28 are allowed.

3. Amendments to claims have overcome prior rejections.

4. The following is an examiner's statement of reasons for allowance. No prior art was found which teaches or fairly suggests a nucleic acid amplification technique that uses two nucleic acid sequences on a single vector as controls to determine the relative copy number ratio of two corresponding nucleic acid sequences. The closest prior art

found was Ginzinger et al. (2002) and Zhang et al. (1997) each of whom teach use of known nucleic acid sequences to determine relative copy numbers of unknown nucleic acid sequences. However, neither Ginzinger et al. (2002) nor Zhang et al. (1997) teach or fairly suggest a control or standard which has two nucleic acid sequences on a single vector.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Close

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARK STAPLES whose telephone number is (571)272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/M.S./
Mark Staples
Examiner
Art Unit 1637
June 5, 2009

/Kenneth R Horlick/

Primary Examiner, Art Unit 1637